R E M A R K S

Claim Amendments

The amendment to claims 1 to 4 to insert the terminology "used as a primer" after the term "oligonucleotide" is supported on page 5, line 12 of the specification.

Rule 116

Entry of the above amendments is respectfully requested, since such claim amendments serve to reply to a 35 USC 112, second paragraph rejection which was raised for the first time in the November 5, 2009 Final Rejection.

Rejection Under 35 USC 112, Second Paragraph

Claims 1 to 4 and 20 to 43 were rejected under 35 USC 112, second paragraph, for the reasons set forth in item no. 12 at the top of page 7 of the November 5, 2009 Office Action.

The position was taken in the November 5, 2009 Office Action that the terminology of "for a primer" recited in claims 1 to 4 renders claims 1 to 4 and 20 to 43 indefinite.

Claims 1 to 4 were amended to avoid the 35 USC 112, second paragraph rejection.

Accordingly, withdrawal of the 35 USC 112, second paragraph rejection is respectfully requested.

Obviousness Rejections Under 35 USC 103

Claims 1 to 4, 23, 29 and 41 were rejected under 35 USC 103 as being unpatentable over Morita et al., Bioorganic & Medicinal Chemistry letters, 12, (2002), 73-76; Braasch et al., Chemistry & Biology, 8, (2001), 1-7 and Orum et al., Clinical Chemistry, 45:11, 1898-1905, (1999) for the reasons indicated in item no. 8 on pages 4 to 5 of the November 5, 2009 Office Action.

Regarding claims 1, 2, 23 and 29, it was admitted in the previous Office Action of April 29, 2009 that Morita et al. do not specifically teach an ENA unit at the third position from the 3'-end; do not specifically teach the "intended use" of nucleotides complementary to a gene which is a target, a target gene; and do not specifically teach a mutant nucleotide.

It was admitted in the previous Office Action of April 29, 2009 that Braasch et al. and Orum et al. do not specifically teach ENA units. It was also admitted in the previous Office Action of April 29, 2009 that Braasch et al. and Orum et al. do not specifically teach a 2'-O,4'-C-ethylene nucleotide (ENA) unit, and do not specifically teach all of the limitations and

intended uses of the claimed oligonucleotide in a single oligonucleotide.

Claims 12 to 17 and 19 were rejected under 35 USC 103 as being unpatentable over Morita et al., Bioorganic & Medicinal Chemistry letters, 12, (2002), 73-76; Braasch et al., Chemistry & Biology, 8, (2001), 1-7; Orum et al., Clinical Chemistry, 45:11, 1898-1905, (1999); and Weston et al. (USP 6,391,593) for the reasons indicated in item no. 9 on pages 5 to 6 of the November 5, 2009 Office Action.

Regarding claims 12 to 17, it was admitted in the previous Office Action of April 29, 2009 that Morita et al. do not specifically teach an ENA unit at the third position from the 3'-end; do not specifically teach the intended use of nucleotides complementary to a gene which is a target, a target gene; and do not specifically teach a mutant nucleotide.

It was also admitted in the previous Office Action of April 29, 2009 that regarding claims 12 to 17, Morita et al. do not specifically teach a kit.

Claims 20 to 22, 24 to 28, 30 to 40 and 42 to 43 were rejected under 35 USC 103 as being unpatentable over Morita et al., Bioorganic & Medicinal Chemistry letters, 12, (2002), 73-76; Braasch et al., Chemistry & Biology, 8, (2001), 1-7; Orum et al.,

Clinical Chemistry, 45:11, 1898-1905, (1999); and further in view of Stanton, Jr. et al. (US 2001/0034023) for the reasons indicated in item no. 10 on page 6 of the November 5, 2009 Office Action.

It was admitted in the previous Office Action of April 29, 2009 that Morita et al., Braasch et al. and Orum et al. do not teach the limitations of claims 20 to 22, 24 to 28, 30 to 40, 42 and 43.

The presently claimed invention relates to an oligonucleotide having an ENA unit at the third nucleotide from the 3'-end.

As correctly noted on page 4 of the November 5, 2009 Office Action, applicant previously argued that the claimed invention of a 2'-O,4'-C-ethylene nucleotide (ENA) at the third position in an oligonucleotide from the 3'-end would not have been obvious to one of ordinary skill in the art at the time of the claimed invention, due to the advantageous results obtained when the corresponding natural oligonucleotide primer is substituted with ENA in the third position from the 3'-end, which ENA substituted oligonucleotide when used as a primer selectively amplifies the gene of interest (216 base pairs) as compared to the natural

oligonucleotide used as a primer (see pages 27 and 28 of applicant's AMENDMENT UNDER 37 CFR 1.111 filed July 23, 2009).

The following position was taken in the paragraph bridging pages 4 and 5 of the November 5, 2009 Office Action:

> "However, Applicant has not provided any evidence that LNA substitution in the third position from the 3' end of the oligonucleotide would not have the same or similar property as the ENA substitution in the third position from the 3'end of the oligonucleotide, and has not provided any evidence rebutting the teaching that ENA substitution of LNA was known and obvious, prior to the claimed invention. LNA substitution in the third position from the 3' end of an oligonucleotide is taught by Braasch et al. (see Table 3) and Orum et al. further teach oligonucleotides comprising LNA substitutions (entire publication, especially Table 1). The substitution of ENA for LNA is taught by Morita et al. (entire article, especially the Abstract). Thus it would have been obvious to one of ordinary skill at the time of the claimed invention to substitute the ENA of Morita et al. for the LNA of Braasch et al. or Orum et al. to arrive at the claimed invention of an oligonucleotide having an ENA substitution in the third position from the 3' end. And thus Applicant's argument is not persuasive, as Applicant is arguing advantageous results of ENA substitution for natural nucleotides, when the rejection was made on the obviousness of ENA substitution for LNA nucleotides."

For the following reasons, applicant respectfully disagrees with the position taken in the preceding paragraph.

Applicant has provided evidence that LNA substitution in the third position from the 3' end of the oligonucleotide would not have the same or a similar property as ENA substitution in the third position from the 3' end of the oligonucleotide. Applicant has also provided evidence rebutting the allegation that ENA substitution of LNA was known and obvious, prior to the presently claimed invention.

Oligonucleotides that have LNA in the third position from the 3'-end of the oligonucleotide are disclosed in the present specification (please see Reference Example 9 and Reference Example 10 on pages 73 and 74 of the present specification). In Reference Examples 9 and 10, the oligonucleotides have C^{e1p} in the third position from the 3' end. As noted in the last sentence on page 27 of the present specification, C^{e1p} is an LNA unit.

The advantageous results of an oligonucleotide having an ENA unit in the third position from the 3' end compared to an LNA unit in the third position in the 3' end is demonstrated by Test Example 1 beginning at the bottom of page 72 and continuing to page 82 of the present specification. Please see the discussion in the

first and second paragraphs on page 82 of the present specification, which are reproduced as follows:

> "Figure 6 shows an example using Premix EX Taq (manufactured by Takara Shuzo Co., Ltd.) instead of Premix Taq (manufactured by Takara Shuzo Co., Ltd.). In this case also, when a primer wherein an ENA unit had been introduced into the third position from the 3'-end thereof was used, almost no non-complementary binding took place, and when the primer of Example 1 was used, the gene was amplified more efficiently and selectively.
>
> The fluorescence intensity of the detected band was converted into a numerical value, and it was then plotted, as shown in Figure 7. In the case of the compounds of Reference Examples 9 and 10, an LNA unit was introduced into the third position from the 3'-end thereof. When the compound of Reference Example 10 was used as the forward primer, 15% amplification of the gene due to non-complementary binding was observed. In contrast, when the compound of Example 2, wherein an ENA unit had been introduced into the third position from the 3'-end thereof, was used as a forward primer, only 6% amplification of the gene due to non-complementary binding was observed. Thus, it was revealed that such an ENA unit results in little non-complementary binding, having high selectivity."

Figures 6 and 7, which are discussed in the two preceding paragraphs, are reproduced as follows:

Figure 6

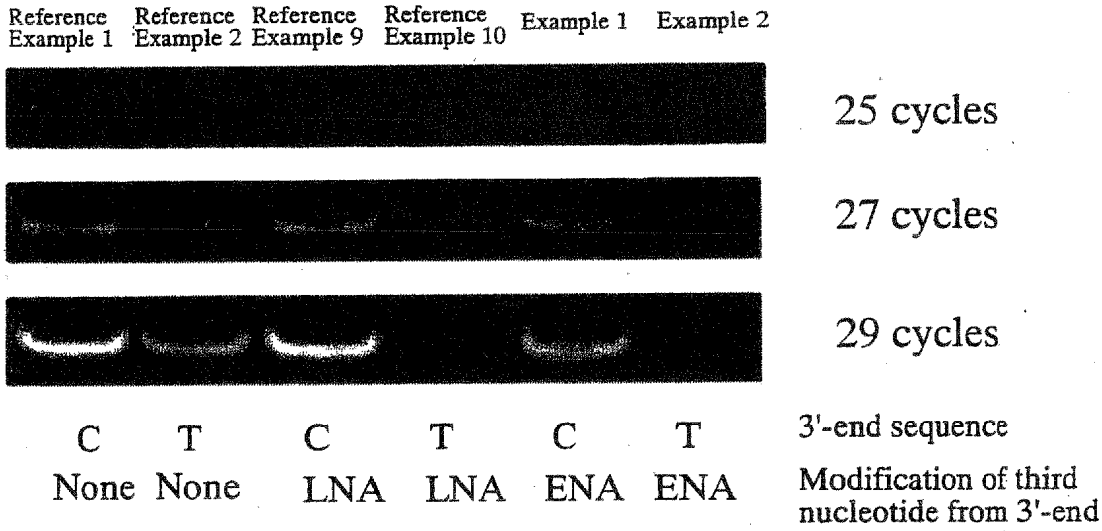
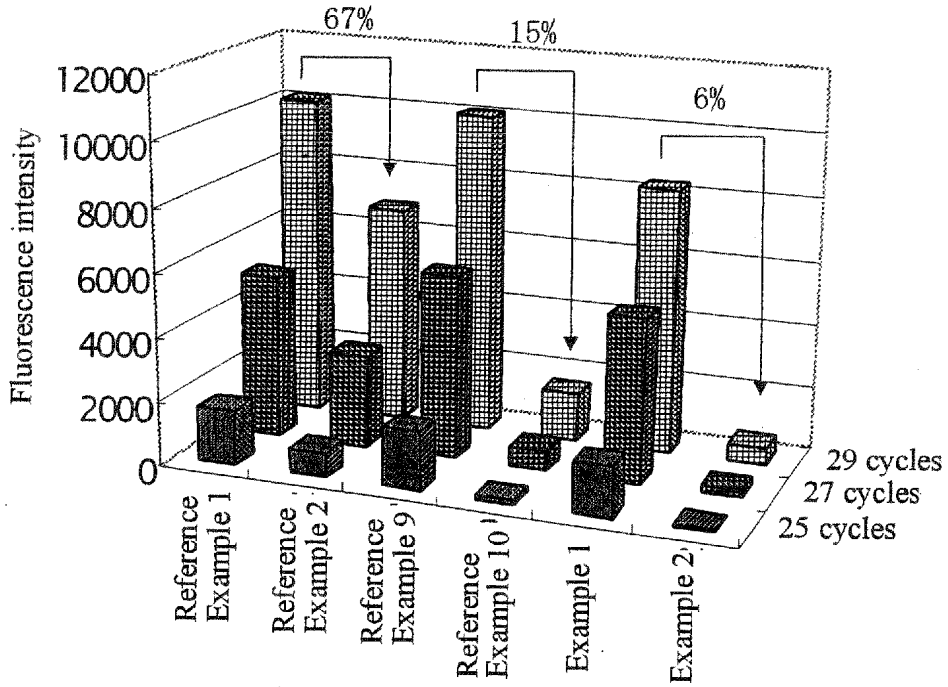


Figure 7



Figures 6 and 7 were explained in the paragraph bridging pages 8 and 9 of the DECLARATION UNDER 37 CFR 1.132 of Makoto KOIZUMI dated January 23, 2009. The aforesaid paragraph from the January 23, 2009 KOIZUMI DECLARATION is reproduced as follows:

> "Heretofore, a serious problem was that significant levels of mismatch extension from the 3' primer:template junction T:G is observed. As shown in Fig. 6 and 7 in the above-identified patent application, in the case of using DNA primers, mismatch extension from the 3' primer:template junction T:G was 67% of match extension from the 3' primer: template junction C:G. On the other hand, when a primer containing a LNA unit at the third position from the 3' end was used, the mismatch extension from the 3' primer: template junction T:G was 15% of match extension from the 3' primer:template junction C:G. Moreover, in the case of using ENA primers containing the ENA unit at the third position from the 3' end, mismatch extension from the 3' primer:template junction T:G decreased to only 6% of match extension from 3' primer:template junction C:G."

It was stated in the previous Office Action of April 29, 2009 that Morita et al. teach oligonucleotides comprising a 2'-O,4'-C-ethylene nucleotide (ENA), which is the second nucleotide from the 3'-end of the oligonucleotide. As shown on pages 27 to 29 of applicant's AMENDMENT UNDER 37 CFR 1.111 filed July 23,

2009, an oligonucleotide having an ENA at the second position from the 3'-end does not provide the advantageous results as an oligonucleotide having an ENA at the third position at the 3'-end, as recited in applicant's present claims.

Braasch et al. disclose many kinds of oligonucleotides having an LNA at various positions and do not particularly specify the position of the LNA. In addition, the oligonucleotide is made for detecting the Tm value, and not for detecting SNPs (single nucleotide polymorphisms).

There is no specific teaching in Braasch et al. concerning inserting a LNA (let alone an ENA) at the third position from the 3'-end of an oligonucleotide.

Orum et al. show the thermostability of octamer oligonucleotides (Table 1). The length of these oligonucleotides are different from the presently claimed invention.

Braasch et al. and Orum et al. do not teach a nucleotide length (i.e., how many nucleotides are in the oligonucleotide?) of the oligonucleotide and where and how many LNAs should be inserted in the oligonucleotide to obtain a oligonucleotide which can detect SNPs.

It is therefore respectfully submitted that Braasch et al. and Orum et al. are completely different from the presently claimed invention.

The following position was taken at the middle of page 30 of the previous Office Action of April 29, 2009:

> "Weston et al. teach kits comprising oligonucleotides with LNA units, DNA polymerases and PCR buffers (see column 7, lines 41 to 51, and see claims 20 and 21)."

Weston et al. do not specify the position and number of LNA units in their probes. In contrast thereto, applicant's claims specify the position (the third position) and number (one) of an ENA unit (the third nucleotide from the 3'-end thereof is a 2'-,4'-ethylene nucleotide (ENA) unit, wherein the nucleotide at the 3'-end is defined as the first nucleotide).

In addition, Weston et al. disclose a kit which comprises a following pair of probes:

(a) first probe: comprising a portion complementary to the sequence of interest and capable of hybridizing thereto, and a portion non-complementary to the sequence of interest;

(b) second probe: comprising a portion complementary to the sequence of interest and capable of hybridizing

thereto, and a portion non-complementary to the sequence of interest, but complementary to that portion of the first probe which is non-complementary to the sequence of interest.

The structure of said pair of probes in Weston et al. is completely different from applicant's claims. It is therefore respectfully submitted that Weston et al. do not teach or suggest applicant's claimed kits.

The following position was taken at the middle of page 31 of the previous Office Action of April 29, 2009:

"Stanton, Jr. et al. teach oligonucleotide/primers for detecting drug metabolizing."

Stanton, Jr. et al. do not teach or suggest an oligonucleotide as recited in applicant's claims (the third nucleotide from the 3'-end thereof is a 2'-O,4'-ethylene nucleotide (ENA) unit, wherein the nucleotide at the 3'-end is defined as the first nucleotide) for detecting drug metabolizing genes.

Stanton, Jr. et al. do not disclose a method for identifying SNPs by using the oligonucleotides, as recited in applicant's presently claimed invention.

It is therefore respectfully submitted that a person having ordinary skill in the art would not consider to combine the references in the manner set forth in the Office Action.

Even assuming *arguendo* that the references are combinable, it is respectfully submitted that one of ordinary skill in the art would not arrive at applicant's present claims in view of the disclosure of the references.

Withdrawal of each of the obviousness rejections is thus respectfully requested.

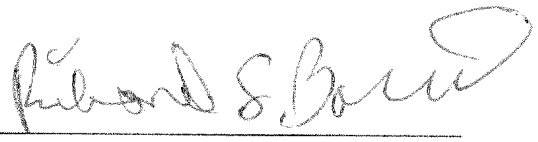
Rejoinder

If the claims of elected Group I are allowed, rejoinder and allowance of the withdrawn claims of non-elected Group II are respectfully requested (see item no. 3 on pages 4 to 5 of the November 5, 2007 Office Action).

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,



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